Diagnostic biomarker for the differential diagnosis of dementia with Lewy bodies

IGTP
Institut de Recerca Germans Trias i Pujol

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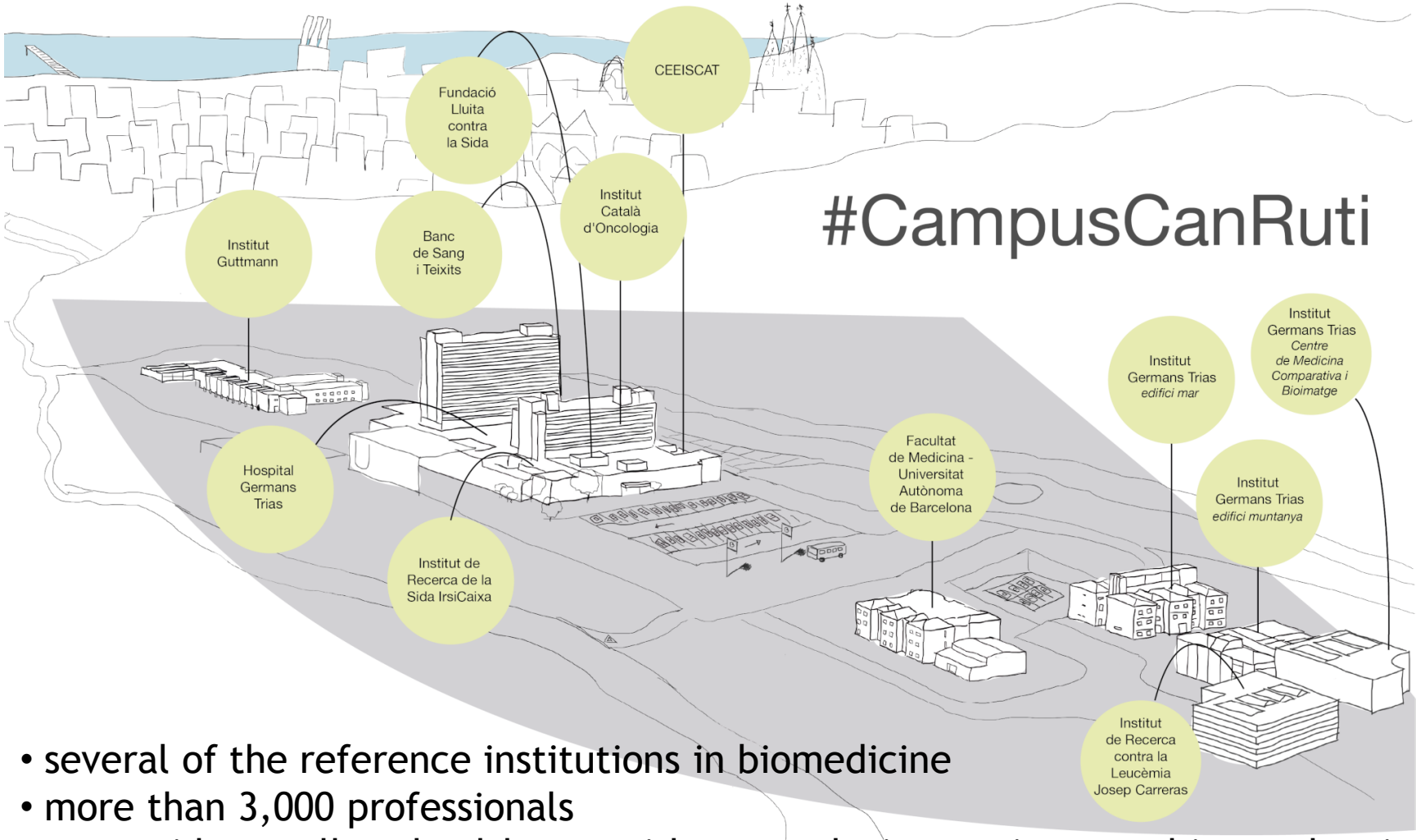
1. The Institution

• Institute for Health Science Research Germans Trias i Pujol (IGTP)

→ public research centre in Catalonia
→ dedicated to increasing scientific knowledge
→ transferring it to improve the care and lives of patients

• IGTP is attached to the Germans Trias University Hospital (HUGTP)
• located on the biomedical campus: Campus Can Ruti.

1. The Institution



- several of the reference institutions in biomedicine
- more than 3,000 professionals
- to provide excellent healthcare with research, innovation, teaching and training

1. The Institution

• IGTP
→ CERCA centre; a member of the biocluster supported and supervised by the Autonomous Catalonian Government
→ accredited by the Instituto de Salud Carlos III since 2008 as a centre of excellence
→ affiliated with the Autonomous University of Barcelona and the Germans Trias Teaching Unit of the Faculty of Medicine

• over 500 papers a year,
• contribute to improved treatment and healthcare protocols
• produce patents
• set up spin-off companies

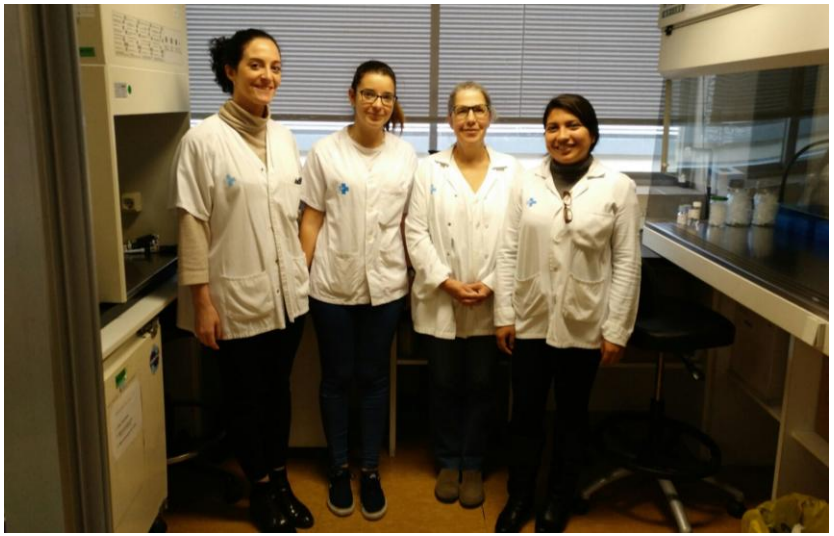
→ all in order to improve the lives of patients

1. The Institution

Research line lead by K Beyer

Genomics & Transcriptomics of Synucleinopathies

1 PhD student
1 technician
2-3 Master students/year

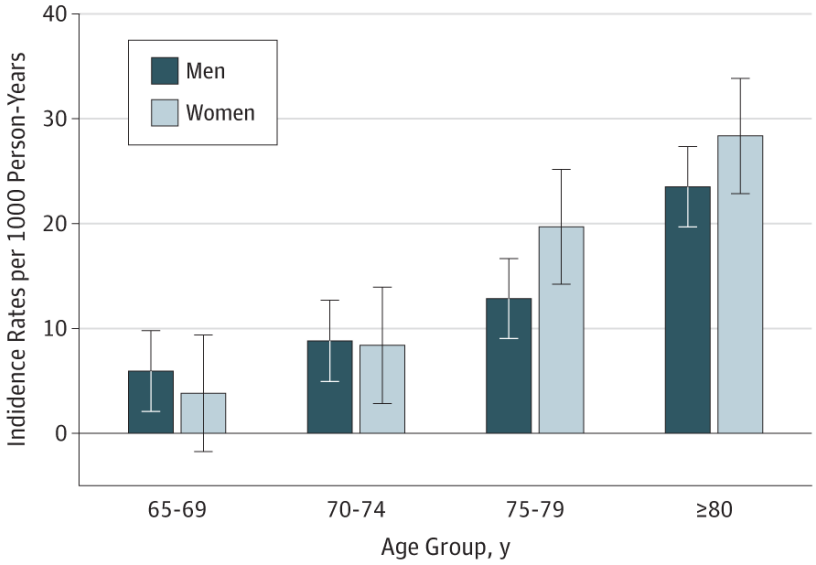


Main objectives

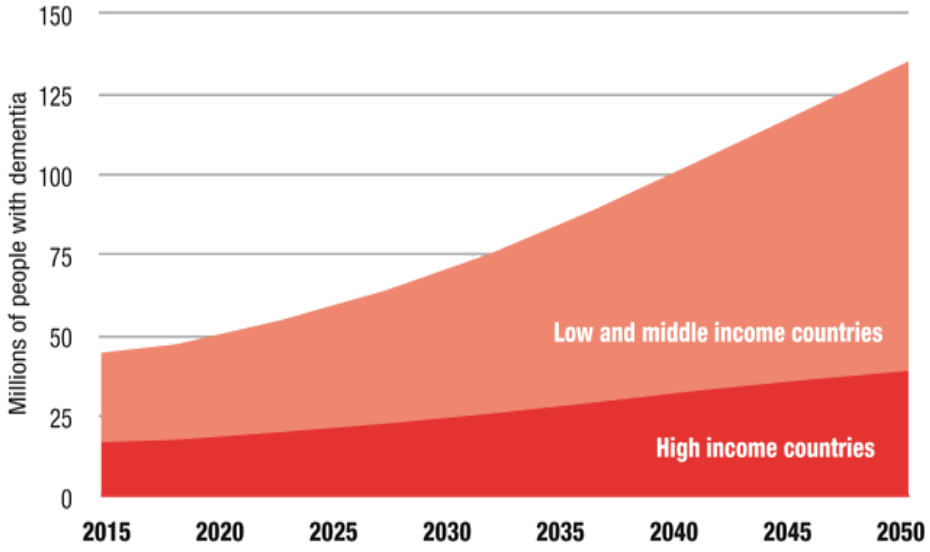
1. Molecular characterization of dementia with Lewy bodies
2. Identification of diagnostic biomarkers for dementia with Lewy bodies

2. The Product – (a) Target Indications

1. Incidence and prevalence of dementias increase with age



2. The world population ages, therefore the number of dementia patients will increase more than twice over the next 30 years



2. The Product – (a) Target Indications

SYNUCLEINOPATHIES

PD - Parkinson's disease

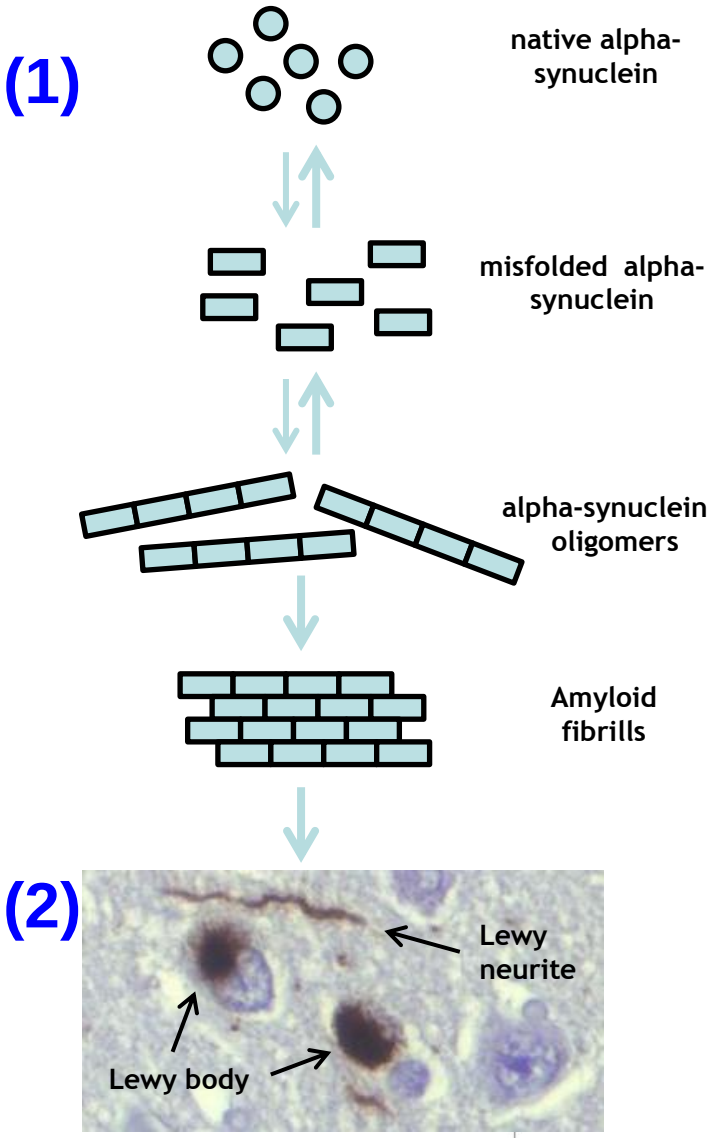
DLB - Dementia with Lewy Bodies

MSA – Multiple system atrophy

Primary pathological MoA

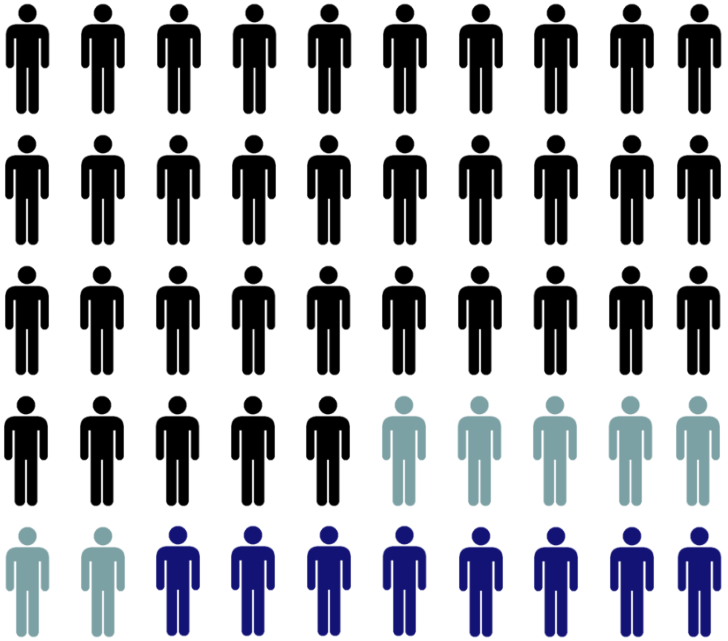
1. Alpha-synuclein oligomerization and aggregation

2. Formation of intraneuronal inclusion bodies



2. The Product – (a) Target Indications

AD and DLB
Clinical & Neuropathological overlap



100% Dementias

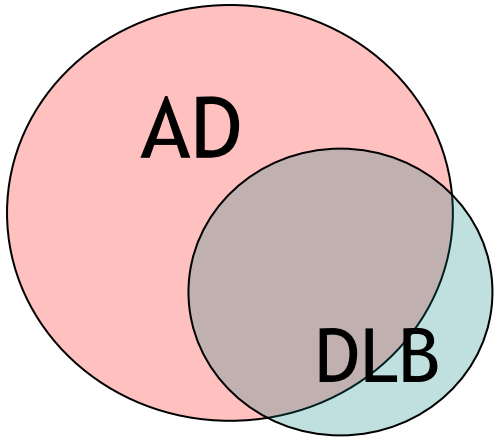
20-30% DLB

Cost: 32.000€/person x year

Misdiagnosis and AD therapy

10-15% SAE

Cost: 7.500€/hospitalization



people with DLB:
10M worldwide, **8M** EU, 400.000 Spain (70.000 new cases yearly)

2. The Product – (b) Innovative mechanisms of action

1- Differential diagnosis of DLB versus AD

→ second most common type of degenerative dementia (20-30% of all cases)

→ up to 80% of all DLB patients are misdiagnosed

→ very heterogeneous and complex disease

BIOMARKER-1: detection of a miRNA absent in DLB but expressed in AD

2- Early / prodromal diagnosis of DLB

→ neurodegeneration by abnormal alpha-synuclein aggregation and oligomerization – starts up to 20 years before clinical diagnosis

→ prodromal DLB (and PD) = idiopathic REM sleep behavior disorder

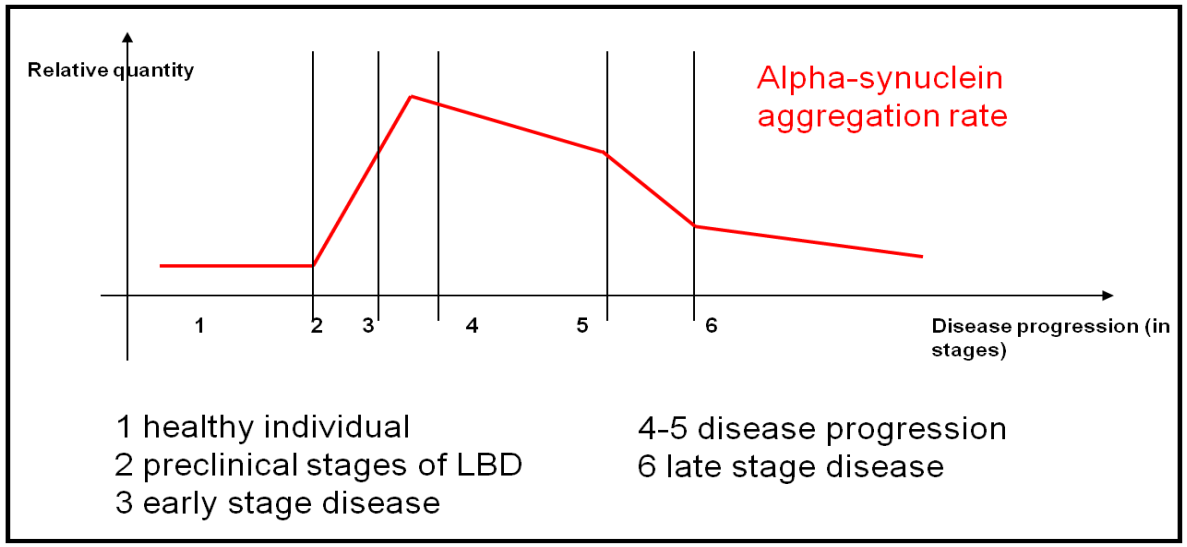
→ prodromal DB (and AD) = subjective cognitive decline (SCD)
= mild cognitive impairment (MCI)

BIOMARKER-2: is aimed to be applied in disease groups that may represent the prodromal stage of DLB.

2. The Product – (b) Innovative mechanisms of action

3- neurodegeneration by abnormal alpha-synuclein aggregation and oligomerization – starts up to 20 years before clinical diagnosis

Development of Lewy pathology over time



BIOMARKER-2: may be indicative for the alpha-synuclein aggregation rate in the brain

2. The Product – (c) Differential features facing the market

• there are NO peripheral biomarkers
→ neither for the clinical
→ nor for the predictive diagnosis of DLB available

• Currently: DaTScan
= radioimaging technique, visualizes dopamine degeneration in the nigro-striatum
→ mostly employed diagnostic tool for the differential diagnosis between DLB and AD
• expensive and invasive
• not always available
→ excludes DaTScan as a common diagnostic tool

2. The Product – (c) Differential features facing the market

1. BIOMARKER-1 (diagnostic biomarker) – to be used in the **clinical practice** for the **diagnosis of DLB;**
differential diagnosis of DLB versus AD.

2. BIOMARKER-1 - stratification of patients → **inclusion in clinical trials**

3. BIOMARKER-2 as a predictive biomarker → early diagnosis of DLB in populations at risk
• early identification of DLB patients
→ development and testing of preventive therapies

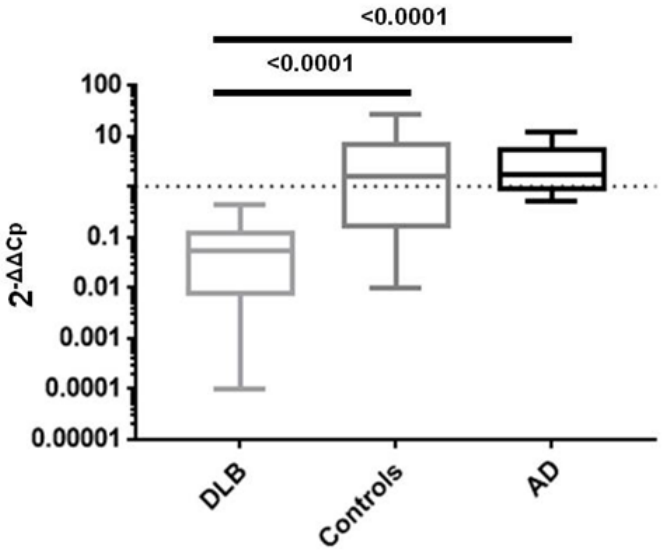
4. BIOMARKER-2 – evaluation of the active AS aggregation process in the brain

2. The Product – (d) Current status of development

BIOMARKER-1: Diagnostic Biomarker

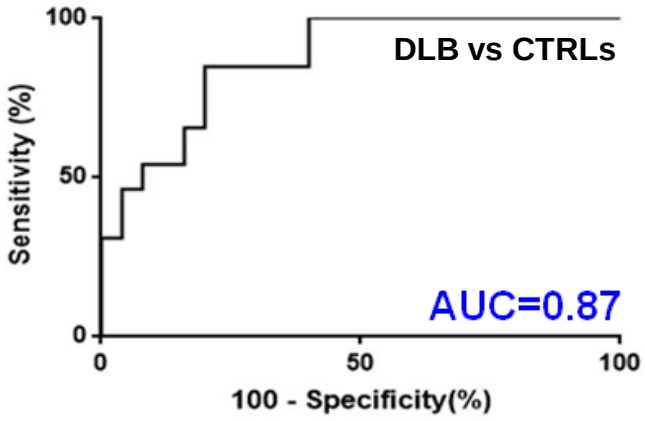
- Differential diagnosis between DLB and AD
- Patient stratification for inclusion in clinical trials
- miRNA expression in platelets
- Whole blood sample

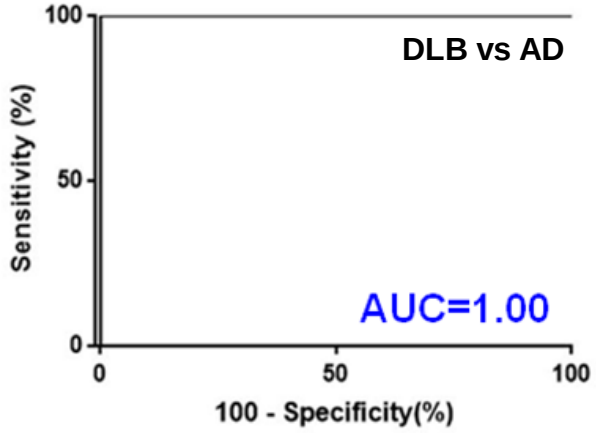
2. The Product – (d) Current status of development



Platelet-miRNA expression in DLB, AD and controls

Results of 2 validation studies



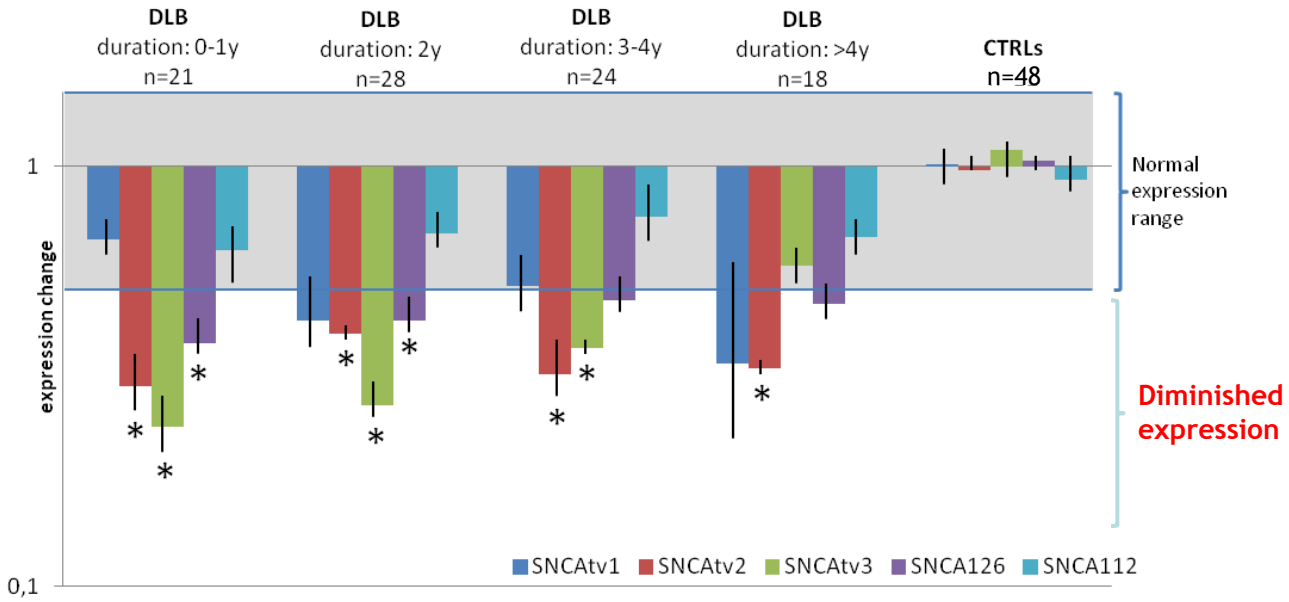


2. The Product – (d) Current status of development

BIOMARKER-2: Predictive Biomarker

- Biomarker for the early / prodromal diagnosis of DLB
- Associated with the alpha-synuclein aggregation rate in the brain
- Whole blood sample

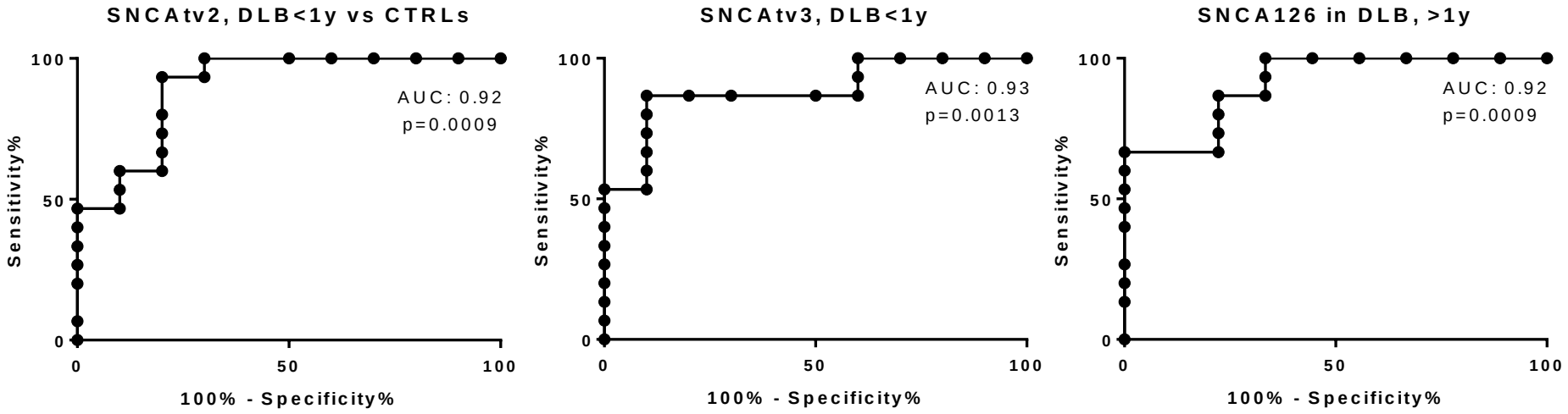
2. The Product - (d) Current status of development



SNCA transcript expression in whole blood of DLB and controls (3 validation studies)

1. SNCA transcript expression varies in dependence on disease evolution.
2. SNCAtv2, SNCAtv3 and SNCA126 are diminished up to 2 years of DLB duration.
3. SNCAtv2 is constantly diminished
4. At advanced disease stages, 4 out of 5 SNCA transcripts show normal expression

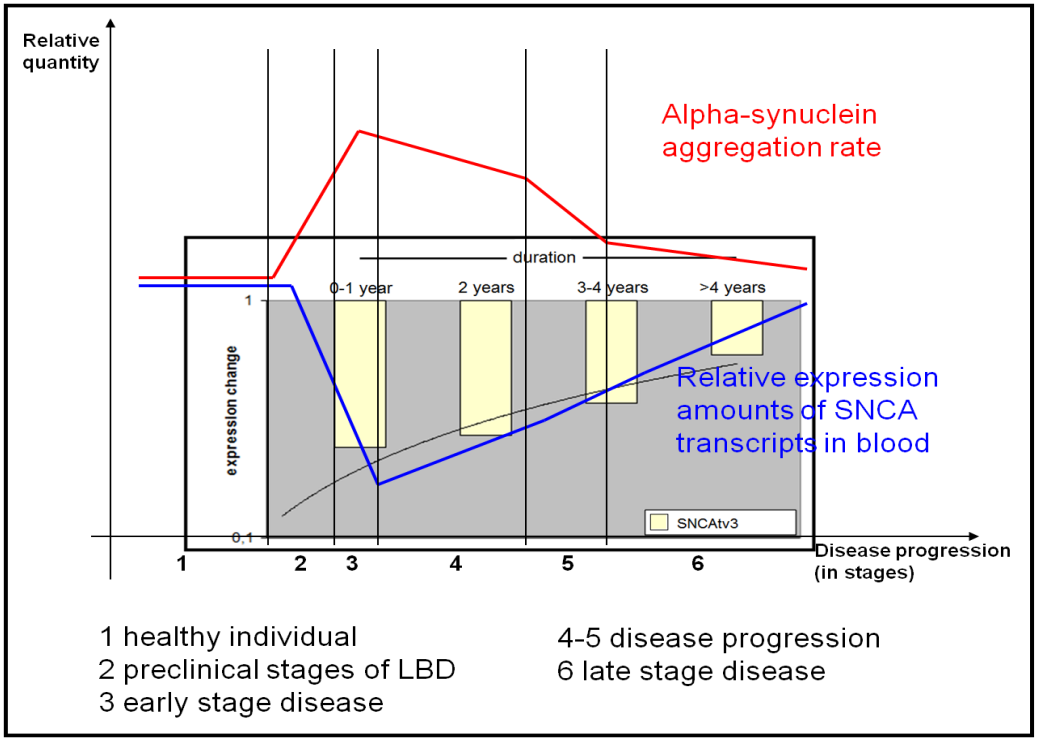
2. The Product - (d) Current status of development



SNCA transcript expression in whole blood of DLB and controls (3 validation studies)

- ROC-curve analyses provided areas-under-the-curve values of:
- 0.92 for SNCAtv2 expression
- 0.93 for SNCAtv3 expression
- 0.92 for SNCA126 expression, all in DLB patients with recent disease onset

2. The Product – (d) Current status of development



- Expression levels of SNCAtv3 in blood → inversely correlate with the alpha-synuclein aggregation rate in brain

- Expression levels of SNCAtv3 in blood → indicate how effective potential anti-aggregation treatments are

2. The Product – (e) IPR protection

Biomarker-2 – Patent 1: METHOD FOR IN VITRO DIAGNOSIS OF DEMENTIA WITH LEWY BODIES USING ALPHASYNUCLEIN GENE TRANSCRIPTS
REGISTRATION: **EP15382241.6**
European Patent Application date: 06/05/2016
Stage of prosecution: National Phase

Biomarker-1 – Patent 2: IN VITRO METHOD FOR THE DIAGNOSIS OF SYNUCLEINOPATHIES
REGISTRATION: **EP18382540.5**
European Patent Application date: 19/07/2018
Stage of prosecution: European patent application

2. The Product – (f) Pitfalls & Risks to be considered

Potential risks

- DLB is a relatively new disease
- Fail to demonstrate clinical efficacy due to heterogeneity of dementia patient
- Fail to demonstrate predictive value of the biomarker
- Fail to demonstrate correlation with alpha-synuclein aggregation rate
- Fail to find the necessary funding for clinical validation

3. Partnering Opportunities

1. **License-out agreement**
2. **Co-development agreement**
3. **Service** offer as service to stratify patients in dementia clinical trials
    1. Clinical trials with validating anti-aggregation of alpha-synuclein
    2. Clinical trials to stratify DLB vs AD

GRACIAS

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